

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit	: 1651	Customer No.:	035811
Examiner	: Susan E. Fernandez		
Serial No.	: 10/695,574		
Filed	: October 28, 2003		
Inventor(s)	: Denis Barritault	Docket No.:	1003-DIV-01
	: Jean-Pierre Caruelle		
Title	: PROCESS FOR TREATING FIBROSES	Confirmation No.:	4857
	: WITH BIOCOMPATIBLE POLYMER		

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**DECLARATION OF DULCE PAPY-GARCIA UNDER 37 C.F.R. 1.132**

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I hereby declare as follows:

1. I, Dulce PAPY-GARCIA, am a Pharmacist, PhD in Organic Chemistry, and full University Professor in Sugar Chemistry and Biochemistry. A copy of my curriculum vitae is attached hereto as Exhibit A.

2. I have read and understood US patent application serial no. 10/695,574 (the "Application"), and have read the Office Action concerning the Application mailed on July 5, 2005.

3. The June 1, 2007 Official Action states that the Application supposedly does not contain sufficient teachings to allow one of ordinary skill in the art to make and use AXY polymers as defined by the Application claims, except for those specifically disclosed in the Application. Thus, I understand that the Examiner believes that the Application does teach one skilled in the art how to make and use AXYZ polymers where A is  $-(O-CH_2-CH_2-CO)-$  or glucose; X is  $-COOH$ ,  $-COONa^+$ ,  $-CH_2COOH$ , or  $-CH_2COONa^+$ ; and Y is  $-CO-CH_2-CHOH-CH_2-SO_3H$ ,  $-CO-CH_2-CHOH-CH_2-SO_3Na^+$ ,  $-SO_3H$  or  $-SO_3Na^+$ ; and Z is phenylalanine or tyrosine. The July 1, 2007 Official Action also states that the Application supposedly does not adequately describe all AXYZ polymers encompassed by the Application claims, but again describes only those polymers which are specifically disclosed.

4. I consider one of ordinary skill in this art to be someone with a PhD degree in Organic or sugar chemistry applied to polymer chemistry, and/or who has about 5 years relevant working experience in Organic or Sugar Chemistry applied to Polymer Chemistry.

5. Concerning how to make AXYZ polymers, I consider that the information contained in the Application is sufficient to allow one of ordinary skill in the art to make the claimed AXYZ polymers, and not only those specifically disclosed in the Application. The information contained in the application should be sufficient to prepare polymers at least of the general formula:  $A_{sub.a}X_{sub.x}Y_{sub.y}Z_{sub.z}$ .

6. The teachings of the Application do convey to one of ordinary skill in the art how to make and use the full range of polymers encompassed by the Application claims. For example, Examples 1 and 2 on pages 22 and 29 of the Application, respectively, show the synthesis of AXYZ polymers in which A is  $-(O-CH_2-CH_2-CO)-$  or glucose. One of ordinary skill in the art would have understood, as of the Application filing date, that other sugars could also be used in the disclosed synthesis scheme with little or no modification to produce the claimed AXYZ polymers. The substitution of other sugars into the synthesis scheme could be readily accomplished with only routine experimentation by one of ordinary skill in the art.

7. Concerning the group A in the XYZ polymers: The application describes: "*A as a monomer, which can be identical or different, selected from the group consisting of sugars, esters, alcohols, amino acids and nucleotides.*" I consider that with the information contained in the application, together with their own knowledge, one of ordinary skill in the art can prepare polymers XYZ wherein A is a sugar unit, (corresponding to any sugar unit, not only glucose, but galactose, xylose, manose, etc.) in a polysaccharide and where A can be different sugars, as in the saccharidic moiety of glycoproteins or in other glycans. I consider that the information contained in the application is sufficient to allow one of ordinary skill in the art to prepare polymers XYZ wherein A can also be a molecule bearing alcohols groups, as polyalcohols.

8. Concerning the group X: The application describes: "*X represents a carboxyl bearing group (-R-COO-R', in which R is a bond or an aliphatic hydrocarbon chain, optionally branched and/or unsaturated, and which can contain one or more aromatic rings except for benzylamine and benzylamine stalfonate, and R' represents a hydrogen atom or a cation*". I consider that with the information contained in the application, together with their own knowledge, one of ordinary skill in the art can make polymers XYZ wherein X represents a carboxyl bearing group (-R-COO-R') in which R is an alkyl ( $R = -[CH_2]_n$ , where  $n \geq 1$ ), an allyl ( $R = -CH=CH[CH_2]_n$ , where  $n \geq 1$ ), aryl, linear or branched groups and R' is a hydrogen atom or a cation.

9. Concerning the group Y: The application describes: "*Y represents a sulfate or sulfonate group bonded to monomer A and is contained within a group according to one of the following formulas: -R-O-SO.sub.3-R', -R- -SO.sub.3-R, -R--SO.sub. 3--R', in which R is a bond or an aliphatic hydrocarbon chain, optionally branched and/or unsaturated, and which can contain one or more aromatic rings except for benzylamine and benylamine sulfonate, and R' represents a hydrogen atom or a cation,*". I consider that with the information contained in the application, together with their own knowledge, one of ordinary skill in the art can make polymers XYZ wherein Y represents a sulfate group bonded to monomer A according to the following formula: -R--SO.sub.3--R' in which R is a bond, an alkyl ( $R = -[CH_2]_n$ , where  $n \geq 1$ ), allyl ( $R = -CH=CH[CH_2]_n$ , where  $n \geq 1$ ), aryl, linear or branched groups.

10. Furthermore, concerning the additional group Z: The application describes: "*Z is a substance different from X and Y, which confers on the polymer additional solubility or lipophilic properties, supplementary biological or physicochemical properties, or a therapeutic or diagnostic agents.*" The Application states also that "*Z can be identical or different, and selected from the group consisting of amino acids, fatty acids, fatty alcohols, cerumides or derivatives thereof and nucleotide addressing sequences.*" I consider that with the information contained in the application, together with their own knowledge, one of ordinary skill in the art can make polymers XYZ in where Z can be identical or different, and selected from the group consisting of amino acids or derivatives thereof.

11. Thus, one skilled in the art would understand from their own knowledge and the teachings of the Application that substitution of the X, Y, and Z components as claimed would not alter the reaction chemistry as disclosed throughout the Application, and in Examples 1 and 2 in particular. The Application therefore contains sufficient teaching to allow one of ordinary skill in the art to make and use the XYZ polymers claimed in the Application.

12. I consider that one of ordinary skill in the art would also be able to quickly envision the various XYZ polymers encompassed by the Application claims, and would understand that such polymers could be made by the disclosed synthetic schemes or by employing routine techniques known to those of ordinary skill in the art. For example, the applicants state that the XYZ polymers can contain  $-(O-CH_2-CH_2-CO)-$  or any sugar as the A component, and one of ordinary skill in the art would understand that any sugar could be readily substituted into the disclosed synthetic schemes without significantly altering the reaction chemistry. Given the Application's disclosure, in particular Examples 1 and 2, one of ordinary skill in the art could also readily envision the specific XYZ polymers formed by using sugars other than glucose in the disclosed reaction schemes. Likewise, substitution of other groups for the X and Y components as discussed above is disclosed in the Application, and one of ordinary skill in the art would understand that these groups could be readily substituted into the claimed XYZ polymers without significantly altering the reaction chemistry, and could readily envision the resultant XYZ polymers. Thus, one of ordinary skill in the art would understand that the

Applicants had possession of the entire claimed range of XYZ polymers as of the Application filing date.

13. The June 1, 2007 Official Action also states that the Application supposedly does not provide one of ordinary skill in the art with a reasonable expectation that administration of the claimed XYZ polymers would successfully treat or reduce fibrosis *in vivo*. The Application presents *in vitro* data which shows that the claimed XYZ polymers inhibit the growth of fibrosis-forming cells such as smooth muscle cells, fibroblasts or hepatic cells, and restore the quantity and quality of collagen produced by such cells under conditions expected to induce fibrosis (e.g., radiation) to that of control cells. See, e.g., Examples 12 and 13 and Figs. 23-26 of the Application. One of ordinary skill in the art would interpret the protocol in these examples as providing guidance for testing all of the XYZ polymers for anti-fibrotic effects. Thus, one skilled in the art in view of the specification would be enabled to use the claimed XYZ polymers to treat fibroses according to the protocol in the specification.

14. I further consider that the evidence presented in the post-filing publications of Mangoni et al., Professor Denoix, and Dr. Aebischer as indicating that the use of XYZ polymers in treating fibroses is not limited to RGTA 1112 and 1113.

15. The Mangoni et al. study was published as an abstract during the 12th European Cancer Conference Organization and is currently under submission for further publication. This Declaration describes both the unpublished study and the published abstract.

16. The unpublished Mangoni et al. study applies the general *in vitro* protocol described in Examples 12 and 13 of the Applicants' specification to an *in vivo* setting. This study not only confirms the *in vivo* efficacy of the *in vitro* protocols described in the Applicants' specification, but also serves as a post-filing confirmation that one skilled in the art could make and use the XYZ polymers recited in the rejected claims. Indeed, the study demonstrates that the anti-fibrotic activity of XYZ polymers is not limited to RGTA 1112 and RGTA 1113, but is also possessed by other species of the genus identified in the rejected claims. Thus, one of

ordinary skill in the art would understand that the Applicants' specification is sufficiently enabling for the entire claimed range of XYZ polymers.

17. In the unpublished Mangoni et al. study, the authors investigated the response of radiation-induced mucositis, a form of fibrosis, to the administration of OTR4131. OTR4131 is an XYZ polymer where A is glucose, X is carboxymethyl, Y is sulfate, and Z is acetate. An experimental group of mice were injected intraperitoneally with OTR4131 at 1mg/kg. Labial mucosas of mice treated with OTR4131 and an untreated control group were isolated from mice 9 and 19 days after irradiation with a single dose of 16.5 Gy. Tissue specimen were washed in 0.9% NaCl and fixed in 10% PBS-buffered formalin for 24 hours, then imbedded in paraffin and sectioned into 5 to 6  $\mu$ m thick cross-sections. Slides were stained with haematoxylin and eosin to measure epidermis depths and inflammatory infiltration. Masson staining was used to measure changes in collagen and epidermis. Frozen samples of 4 $\mu$ m thick tissue that were fixed with acetone and stained with May-Grunwald and Giemsa were used to count leukocytes.

18. Mangoni et al. demonstrates that labial mucosas treated with OTR4131 and isolated from mice 9 days after irradiation had reduced tissue thickness, collagen secretion, and leukocyte infiltration compared to untreated samples (See Fig. 4 of Mangoni et al.). Tissue samples treated with OTR4131 and collected 19 days after irradiation were indistinguishable from non-irradiated samples with respect to leukocyte count (See Fig. 4 of Mangoni et al.).

19. Mangoni et al. also reported on the effects of OTR4131 on radiation-induced mucositis in the abstract published during the 12th European Cancer Conference Organization. Mice were sprayed with a solution of OTR4131 at 10 $\mu$ g/mL, injected intraperitoneally with OTR4131 at 1mg/kg, and then irradiated with a single dose of 16.5 Gy. Mucosal reactions occurring over 21 days post-irradiation were evaluated according to the Parkins scoring system.

20. The abstract data demonstrates that irradiated mice sprayed with OTR4131, then injected intraperitoneally at 3 hours, 1 day, and every 3 days after irradiation presented with significantly reduced degrees of mucositis than the control group that were irradiated without OTR4131 treatment ( $p < 0.001$ ). Compared to untreated control mice, mice treated with

OTR4131 showed a marked decrease in the severity and duration of mucositis with administration of OTR4131 3 hours after irradiation ( $p=0.0006$ ) and 24 hours after irradiation ( $p=0.001$ ) (See figure published with abstract).

21. Professor Denoix's and Dr. Aebischer's research also demonstrate the *in vivo* anti-fibrotic effects of RGTAs recited in the rejected claims that are different than RGTA 1112 or 1113. Thus, these studies verify that one skilled in the art could make and use the claimed polymers to treat factors related to fibrosis.

22. Professor J. M. Denoix's research at the French National Veterinary School demonstrated that horses diagnosed with tendonitis did not develop fibrotic tissue after an intratendon injection of RGTA OTR4131. OTR4131 is an AXYZ polymer where A is glucose, X is carboxymethyl, Y is sulfate, and Z is acetate. Denoix injected 2.5 mL of OTR4131 at a concentration of 100ug/mL into the superficial digital flexor tendon. Ultrasonography of the treated tendons indicated that tissue density of the diseased tendons regenerated and the organization of the tissue appeared normal.

23. Dr. Aebischer treated horse cornea with OTR4131 and OTR4336 resulted in recovered transparency. Additionally, topical application of OTR4336 in a 100ug/mL solution every three days also prevented the formation of hypertrophic scars at the site of skin ulcers.

24. The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 19 Oct 2007

Signature: \_\_\_\_\_

A handwritten signature, likely of Dr. Aebischer, written in black ink over a horizontal line. The signature is stylized, with a large 'A' and 'E' being prominent.

## **Professor Dulce PAPY-GARCIA**

Pharmacist and PhD in Sciences

Born on September 10th 1966

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### **DIPLOMAS AND CERTIFICATES:**

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|-------------|--|
| <b>1996</b> | <b>PhD Sciences (Organic Synthesis, Sugar Chemistry)</b><br>Tokushima Bunri University, Tokushima, Japan.          |
| <b>1993</b> | <b>Master in Pharmaceutical Sciences (Organic Chemistry)</b><br>Tokushima Bunri University, Tokushima, Japan.      |
| <b>1990</b> | <b>Diploma on the study of the Japanese Language and Culture</b><br>University of Foreign studies of Osaka, Japan. |
| <b>1989</b> | <b>Pharmacist</b><br>School of Chemistry-Pharmacy-Biology<br>University of Michoacan, Mexico.                      |
| <b>1989</b> | <b>Awarder as First Young Pharmaceutical Chemist</b><br>Clinical Chemistry Society, Mexico.                        |

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### **Research and Professional Positions:**

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| <b>From 2005</b> | <b>Head of the Research Group ATIP 'Glycannes. Structure-Function'</b><br><b>Created by the French National Center of Scientific Research (CNRS)</b><br>University Paris 12, Faculty of Science and Technologies, France. |
| <b>From 2004</b> | <b>Full Professor (Biochemistry and Glycosciences)</b><br>University Paris 12, Faculty of Science and Technologies, France.   |
| <b>From 2003</b> | <b>Member of the 'NeuroPrion European Excellence Network'</b>   |
| <b>2001-2004</b> | <b>Assistant Professor (Biological Chemistry)</b><br>University Paris 12, Faculty of Science and Technologies, France.  |
| <b>1997-2001</b> | <b>Project Manager and Researcher</b><br>ValbioFrance Company, Paris, France.   |
| <b>1996-1997</b> | <b>Post-Doct Position (Biopolymer Sciences)</b><br>Ecole Nationale Supérieure de Chimie, Toulouse, France.  |

30 publications in international journals

## **EXHIBIT A**